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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,665	07/13/2001	Giancarlo Santus	6485/16895US2	3102

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EXAMINER	
KRASS, FREDERICK F	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,665	SANTUS ET AL.	
	Examiner	Art Unit	
	Frederick Krass	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 19-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 19-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/383,707.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Case

Judgment favorable to Applicant was rendered under Board Rule 127(b)(4) in an Interference Proceeding decided 07/17/06. The examiner has, following consultation with his supervisor (Ardin Marschel), however, withdrawn the previous determination of allowability concerning the instant claims. New grounds of rejection under 35 USC 112, first and second paragraphs, follow infra. The extension of prosecution is regretted. (Upon allowance, Applicant may wish to consider petitioning for an extension of patent grant based on PTO administrative delay).

This action is NON-FINAL.

Specification: Continuation Status

Applicant is requested to amend the first line of the specification to indicate the status of this case as a continuation of USSN 08/383,707, filed 02/01/1995, now USP 6,333,044, which is a continuation of USSN 07/875,700, filed 04/29/1992, now abandoned.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-22 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No support is seen in the specification as originally filed for reciting "a phospholipid" at the second line of claim 19. Page 6, lines 20-32 of the instant specification states that additional excipients "include chemical enhancers such as absorption promoters", and lists a variety of chemically divergent and unrelated species such as chelating agents, fatty acids, preservatives, *etc.* as examples thereof. "Lyophosphatides" such as "lysophosphatidyl-choline" are exemplified; no other "phospholipids", however, are enumerated. This disclosure of a single subgenus of a very specific type of phospholipid does not reasonably provide support for the entire genus of "phospholipids", a term embracing a vast number of divergent species.

Insufficient Written Description Rejection

Claims 19 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 19 and 25 recite nasal sprays comprising an effective amount of a ketorolac "-based" analgesic. The specification uses the term "KETOROLAC®-based" in passing at page 7, line 28; it does not appear to have been defined there or elsewhere. Meanwhile, the specification also states:

> Hereinafter, the name KETOROLAC® shall encompass individually or collectively the racemic mixture or either optically active compound and shall encompass the free acid as well as the tromethamine salt or any other pharmaceutically acceptable salt of any one of the foregoing. (Passage bridging page 1, line 39 to page 2, line 3).

While the term "ketorolac" has been adequately defined, the term "-based" has not. It is impossible to determine from the disclosure as originally filed which compositions, other than those containing the compound ketorolac, its optical isomers, or salts thereof, are ketorolac"-based." (For example, a high molecular weight poloxyalkylene ester of ketorolac would be "ketorolac-based", but no such species is described. Many other unspecified derivatives could theoretically be included as well).

In order to obviate this ground of rejection, the examiner recommends deleting the phrase "ketorac-based" in claims 19 and 25 and inserting after the term "analgesic" --- comprising ketorolac, an optical isomer thereof, or a salt thereof ---.

Scope of Enablement Rejection

Claims 19-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for aqueous nasal sprays comprising ketorolac (and its optical isomers and salts) and a bioadhesive polymer selected from the group consisting of polyacrylics and carboxymethylcellulose, which when administered intranasally to mammals in amounts ranging from between 0.5 mg/kg/day and 4 mg/kg/day will generate plasma levels of ketorolac within the range of 0.3-5 mg/liter of plasma, does not reasonably provide enablement for such nasal sprays generally (*e.g.*, non-aqueous compositions) which "when administered intranasally" provide "a therapeutic blood level comparable to that of the same formulation when injected." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the

> specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to nasal sprays containing ketorolac.

The relative skill of those in the art is high, that of an MD or PHD. That factor is

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498, 504 (CCPA 1976), the key word is "undue", not "experimentation".

outweighed, however, by the unpredictable nature of this art.

By Applicant's own admission:

> The ability of drug molecules to be absorbed by the nasal mucous membrane in utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes. (Specification, page 4, lines 6-9; emphasis added).

This admission reflects the state of the art at the time of filing. See, *e.g.*, USP 5,122,127 to Stanley et al. Note especially the disclosure of column 13, lines 13-15, wherein patentee states:

> It is almost impossible to predict which enhancer will work best for a given drug. For each individual drug, only experiments can tell which enhancer is the most suitable. (Emphasis added).

Thus, the art of formulating compositions for nasal administration is not simply unpredictable; it is in fact completely unpredictable. Recalling that scope of enablement varies inversely with the degree of unpredictability, this means the burden on Applicant to provide reasonably sufficient direction to make the instantly claimed formulations will be very high.

2. The breadth of the claims

The instant claims are drawn to nasal sprays containing a "ketorolac-based" analgesic and a bioadhesive, said sprays "when administered intranasally" providing "a therapeutic blood level comparable to that of the same formulation when injected."

This purely functional limitation is not accompanied by any concurrent recitation of the host to which it is administered, the time period over which the blood level is

measured, *etc.* Furthermore, no relative concentrations are recited. The claims are thus extremely broad, encompassing a) compositions containing any type of solvent or bioadhesive and b) compositions exhibiting such behavior over such a wide range of formulations as to render the functional limitation basically non-limiting. A highly concentrated nasal spray could provide the same bioavailability as a very dilute injectable composition, for example. Similarly, without knowing the time period at which/over the blood levels are measured, the functional limitation is likewise meaningless. A nasal spray could provide the same blood level as a parenteral composition if blood levels for the former were measured after a period of time had elapsed, while those of the latter were measured immediately following injection. Without knowing the relative concentrations, volumes administered, times at which measurements were made, *etc.*, such parameters could be manipulated so that almost any nasal spray could (in theory) be argued to be capable of providing a therapeutic blood level "comparable" to the "same" formulation when injected.

In order to obviate issue "b)", the examiner recommends adopting a more concrete, measurable and reproducible parameter, *e.g.*, reciting a "spray which when administered intranasally to mammals in amounts ranging from between 0.5 mg/kg/day and 4 mg/kg/day will generate plasma levels of ketorolac within the range of 0.3-5 mg/liter of plasma" as disclosed at the first paragraph of page 5 of the instant specification.

3. The amount of direction or guidance provided and the presence or absence of working examples

The compositions tested in the instant working examples are aqueous CMC and acrylic polymer solutions. As noted by Applicant at page 5, lines 28-31, these are species having unusually high degrees of bioadhesiveness. (Similarly, "Lutrol F127", a poloxamer also used in the working examples, forms thermoreversible gels upon application and thus is also unusually bioadhesive).

These are the only particular compositions which have been specifically demonstrated to provide the requisite pharmacologic activity recited. The specification provides no guidance as to which solvents other than water, nor which other bioadhesives, could reasonably be expected to impart the same highly unexpected activity.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instant generally claimed "ketorolac-based" nasal sprays could be used to provide therapeutic blood levels "comparable to" the "same" formulation when injected as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed

in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Indefiniteness Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1) Claims 19 and 25, the phrase "same formulation" is non-sequitur. The nasal spray cannot possibly be the "same" composition as that which is injected. (It could be a "corresponding" composition, but the not the same one).

2) Claims 19 and 25, "having" a therapeutic blood level is similarly non-sequitur. (The nasal spray could "provide" a desired therapeutic blood level following administration, but it does not *per se* have that characteristic).

3) The term ketorolac"-based" is unclear in meaning for the same reasons outlined in the "Insufficient Written Description" section supra.

Provisional Nonstatutory ("Obviousness-Type") Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 25 of copending Application No. 10/792,457. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions of the instant claims represent species within the genus of the broader conflicting claims. Furthermore, the instant claims would appear to recite merely inherent characteristics of the conflicting compositions following administration, once the active agent becomes available in the bloodstream. (The examiner notes that conflicting claim 25 recites the composition as being contained in an atomizer. It would have been obvious in a self-evident manner,

however, to have administered a nasal spray via an atomizer, as is typical of commercially available nosesprays).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (571) 272-0580. The examiner can normally be reached on Monday-Friday from 9:30AM to 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frederick Krass
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Art Unit 1614